REMARKS

Prior to amendment, claims 1- 44 were pending. Claims 15, 17-19 and 37-39 have been amended. Claim 16 has been canceled. After amendment, claims 1-15 and 17-44 are pending.

Rejection of Claims Under 35 USC §102(b)

The examiner has rejected claims 1-13, 15, 16, 20-23, 25, 27, 28, 30-36, and 40-42 as being anticipated by Egan et al. US Patent Publication 2002/0177586 ("Egan"). The examiner points out a variety of terms in Egan as support for this rejection, including (a) diseases treatable, (b) drugs that can be delivered in combination with the compounds of the invention, (c) nasal administration, (d) carriers and excipients, and (e) form of the compositions, e.g., sprays and dry powders with propellants.

Applicants respectfully traverse the rejection. Anticipation under 35 USC §102 requires that each and every element of the invention be present in the anticipatory art.

Egan does not anticipate the present claims. Egan teaches a family of compounds, called "first agents" (*see, e.g.,* Summary of the Invention, paragraphs 0007; 0087; and 126 -127), and a wide variety of uses for these compounds. For some of those uses, Egan also teaches combination therapy with other drugs that have previously been used to treat a particular condition. The examiner has cited these references to the secondary set of drugs as anticipating the methods of the present claims. However, each of the secondary drugs must be delivered with at least one of the first agents (*see, e.g.,* paragraphs 126 and 127). For example, Egan states "[i]n treating heart failure, cardiomyopathy or heart attack, **first agents** can be administered concurrently or in combined formulation with one or more ... calcium channel blockers ...." (emphasis added; paragraph 127). Clearly, Egan teaches first and foremost the delivery of a first agent, with the option of adding a calcium channel blocker. The calcium channel blocker is not being delivered alone. If a calcium channel blocker is used, Egan's methods require that a first agent of the invention also be delivered. If the combination of a first agent and a calcium channel blocker were found to work, such as to treat heart failure, cardiomyopathy, or heart attack, one would not be able to discern what aspect of the combination of compounds was causing this effect, because Egan provides no data to show what the effects of the first agents are on the disease. Therefore, this disclosure does not anticipate delivery of a calcium channel blocker alone.

The examiner cites Egan as teaching that the combination of first agents and secondary compounds (e.g., calcium channel blockers) is useful for treating hypertension. Applicants disagree. There are no working examples in Egan of the delivery of the first agents, let alone in combination with the secondary compounds. Egan presents a theory on how the first agents work, extrapolating this to a very wide variety of medical treatments. Egan then suggests combining these first agents with secondary compounds that were previously known to treat some of the conditions. Egan does not either show that the combination works in each case, or even that they can be successfully delivered. Egan fails to even state that calcium channel blockers could be combined with first agents to treat hypertension. Paragraph 0120 does refer to the use of first agents to "treat, prevent, reduce or ameliorate reduced vascular compliance, elevated pulse pressure, and hypertension." However, when discussing combination therapies in paragraph 0127, Egan only refers to treating heart failure, cardiomyopathy, or heart attack.

While Egan discusses nasal delivery (paragraph 0622), Egan does not enable the delivery of calcium channel blockers nasally. None of Egan's examples relates to the delivery of first agents, let alone secondary compounds. Nor is there a teaching on how to nasally deliver the first agents alone or in combination with secondary compounds. There is no data to show that such a form of delivery will actually work with any of these compounds. The inventors of the present invention were the first to deliver calcium channel blockers nasally, documenting the results in their Examples.

The examiner has also referred to numerous locations in Egan as teaching aspects of the dependent claims of the present invention. For example, the examiner cites a pharmaceutically acceptable carrier in paragraph 0616, dosage range in paragraph 0622, and excipients in paragraph 0622. Applicants point out that while these elements may be present in Egan, they are parts of dependent claims in the present application. Thus, they require the presence of all of the elements in the claims from which they depend. As demonstrated above, Egan does not anticipate the independent method claims of the present invention, i.e. claims 1, 24, and 25. Therefore, claims 2-13, 15, 16, and 20-23 are not anticipated by Egan. Applicants request that the examiner withdraw this rejection with respect to claims 2-13, 15, 16, and 20-23.

Rejection of Claims Under 35 USC § 102(e)

The examiner has rejected claims 1, 2, 5-13, 15, 16, 20-36, and 40-42 as anticipated by Krause, US patent publication 2004/0014782 ("Krause"). As with Egan, the examiner points out a variety of terms in Krause as support for this rejection, including (a) diseases treatable, including myocardial infarction, (b) drugs that can be delivered in combination with the compounds of the invention, (c) nasal administration, (d) carriers and excipients, and (e) form of the compositions, e.g., sprays and dry powders with or without propellants.

Applicants respectfully traverse the rejection. Anticipation under 35 USC §102 requires that each and every element of the invention be present in the anticipatory art. Krause does not anticipate the present claims because it does not teach each and every element of the present invention. Krause teaches a family of compounds, called "C5a antagonists," delivered in combination with other drugs that have previously been used to treat a particular condition. (*see, e.g.,* Field of the Invention), and a wide variety of uses for these compounds. The examiner has cited these references to the secondary set of drugs as anticipating the methods of the present claims. However, each of the secondary drugs must be delivered with at least one of the first agents (*see, e.g.,* Field of the Invention, paragraphs 0027 and 0030).

For example, Krause states "Also provided herein are **combinations** useful for the treatment of cardio- and cerebrovascular disease ...." (paragraph 0244; emphasis added). Clearly, Krause teaches the delivery of a C5a antagonist in combination with a secondary set of drugs, which may include a calcium channel blocker. The calcium channel blocker is not being delivered alone. If a calcium channel blocker is used, Krause's methods require that a C5a antagonist also be delivered. If the combination of a C5a antagonist and a calcium channel blocker were found to work, such as to prevent or treat myocardial infarction or restenosis, one would not be able to discern what aspect of the combination of compounds was causing this effect. According to Krause, in some combinations the C5a antagonists would enhance the effect of the calcium channel blocker (paragraph 0265), but no evidence is given that this is true or that it can even be expected. In fact, there is no evidence that C5a antagonists won't have a negative impact on the effects of the calcium channel blockers. Therefore, this disclosure does not anticipate delivery of a calcium channel blocker alone as claimed in the present invention.

The examiner cites Krause as teaching that the combination of C5a antagonists and secondary compounds (e.g., calcium channel blockers) is useful for treating hypertension.

Applicants disagree because Krause does not enable such a teaching. There are no working examples in Krause of the delivery of a C5a antagonist, let alone in combination with a secondary compound, to a mammal. Like Egan, Krause presents a theory on how the C5a antagonists can work in treating disease when combined with a composition previously known to have at least some positive effect on the disease, extrapolating this to a very wide variety of medical treatments. Krause does not either show that the combination works in any case, or even that the combinations can be successfully delivered.

While Krause discusses nasal delivery (paragraph 0303), Krause does not enable the delivery of calcium channel blockers nasally. None of Krause's examples relates to the delivery of C5a antagonists or the secondary compounds alone. Nor is there a teaching on how to nasally deliver the C5a antagonists in combination with secondary compounds. The examiner cites to descriptions of inhalers and nebulizers, and powders and liquids that can be used with these devices. However, inhalers and nebulizers are used to provide compositions to the lungs, not the nasal passages (*see, e.g.,* paragraph 0300). Paragraph 0303 describes supposed methods for nasal delivery of the drug combinations. It states that small particles of the drug combination are "administered in the manner in which snuff is administered, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose." This is hardly an appropriate method for delivering a controlled dose of a drug combination to a patient. There is no data to show that such a form of delivery will actually work with any of these compounds. The inventors of the present invention were the first to deliver calcium channel blockers nasally, documenting the results in their Examples.

The examiner has also referred to numerous locations in Krause as teaching aspects of the dependent claims of the present invention. For example, the examiner cites carriers and excipients in paragraph 0030. Applicants point out that while these elements may be present in Krause, they are parts of dependent claims in the present application. Thus, they require the presence of all of the elements in the claims from which they depend. As demonstrated above, Krause does not anticipate the independent method claims of the present invention, i.e. claims 1, 24, and 25. Therefore, claims 2-13, 15, 16, and 20-23 are not anticipated by Egan. Applicants request that the examiner withdraw this rejection.

Rejection of Claims Under 35 USC § 103(a)

The examiner has rejected claims 3, 4, 14, 17-19, 37-39, and 43-44 as obvious over Krause in view of Wermeling et al. WO 02/13886 ("Wermeling"), Krause alone lacking disclosure on specific devices for nasal delivery of unit dosages. This gap is allegedly filled by Wermeling.

Applicants respectfully disagree that the combination of Krause and Wermeling makes the present invention obvious. As described above, Krause is missing more than a description of a device for nasal delivery of unit dosages. Krause teaches that secondary drugs are provided only in combination with C5a antagonists. If a calcium channel blocker is used, Krause's methods require that a C5a antagonist also be delivered. If the combination of a C5a antagonist and a calcium channel blocker were found to work, such as to prevent or treat myocardial infarction or restenosis, one would not be able to discern what aspect of the combination of compounds was causing this effect. According to Krause, the C5a antagonists would enhance the effect of the calcium channel blocker (paragraph 0265), but no evidence is given that this is true or that it can even be expected. In fact, there is no evidence that C5a antagonists won't have a negative impact on the effects of the calcium channel blockers. Therefore, this disclosure does not anticipate delivery of a calcium channel blocker alone as claimed in the present invention.

Wermeling teaches a device for nasally delivering drugs to a patient. While this may fill one of the gaps in Krause, it does nothing for the other gaps noted above. Therefore, the combination of Krause and Wermeling does not make the present invention obvious. Applicants request that the examiner withdraw this rejection.

Double Patenting Rejection of claims 18, 19, 38 and 39

Applicants have amended claims 17-19 and 37-39 to address the examiner's double patenting rejection. Claims 17 and 37 now relate to controlled release, 18 and 38 relate to sustained release, and 19 and 39 relate to timed release. Claims 18 and 19 now depend from claim 17, and claims 38 and 39 now depend from claim 37. Sustained release and timed release are subsets of controlled release. In light of the amendments, applicants request that the examiner withdraw the double patenting rejection.

CONCLUSION

For the reasons stated above, the claims of the present application are now ready for allowance, and applicants request that the examiner so declare. The examiner is invited to contact the undersigned at (650) 251-7702 if he believes it would aid in the progress of the application.

Respectfully submitted,

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